

Topics and Questions for Panel Discussion

The Plastic and Reconstructive Device Advisory Panel is being asked to address the following four topic areas related to both pre-market and post-market evaluation of dermal filler devices. Additional background information corresponding to each section of questions below is provided in the executive summary.

Safety of dermal filler use in patients with Fitzpatrick Scale Scores IV-VI

A majority of subjects enrolled in clinical studies conducted to support pre-market approval of dermal fillers have Fitzpatrick scale scores of III or below. Several post-market studies for evaluating the safety of dermal filler injections in patients with Fitzpatrick skin types IV-VI have been completed and reviewed by FDA. These post-approval studies were mandated as a Premarket Approval (PMA) condition of approval. The studies assessed the likelihood of incidence of keloid formation, hypertrophic scarring, pigmentation change, and hypersensitivity post-injection. After review of data presented by FDA, you will be asked to discuss the data within the context of the following questions.

1. Have the post-approval study results demonstrated safety of dermal fillers for patients with Fitzpatrick scale scores IV-VI?
2. Based on clinical experience and data collected in these post-approval studies, is there sufficient evidence to conclude that evaluation of safety of dermal fillers in patients with Fitzpatrick scale scores I-III can be used to predict safety of dermal fillers in patients with

Fitzpatrick scale scores IV-VI? If so, would such a conclusion be limited to only the filler materials that have been evaluated in these post-approval studies or would this conclusion extend to new filler materials not previously approved by FDA?

3. Should clinical evaluation of dermal fillers consider patients with Fitzpatrick scale scores I-III and IV-VI as two distinct populations with potential to exhibit different safety profiles?

Post-market evaluation of adverse events reported to FDA

The Office of Surveillance and Biometrics, Division of Postmarket Surveillance, Product Evaluation Branch conducted a review of adverse events related to dermal filler injection that were reported to FDA over a five year period. The adverse events were evaluated to determine the types of adverse events experienced in post-market use as well as the severity of these adverse events. After review of data presented by FDA, you will be asked to discuss the data within the context of the following questions.

4. Current labeling for dermal fillers state that most adverse events are immediately noticeable and temporary.
 - a. Please discuss the adequacy of the current labeling including whether labeling should be modified to include adverse events that may manifest several weeks to several months after the initial injection or those adverse events that may take some time to resolve, such as scarring and necrosis?

- b. Should labeling be modified to include such types of adverse events which were not observed during the clinical study but are evident in post-market adverse event reporting?

5. Considering that dermal fillers, in general, are administered to healthy patients as an elective procedure for aesthetic improvement, should FDA's tolerance for mild to severe adverse events be different than for devices that are intended for treatment of disease? If so, does the panel consider that current FDA tolerance for serious adverse events should be increased or decreased for aesthetic use products?

6. What would be the most effective method or combination of methods for FDA communication to physicians regarding the post-market information collected by FDA, such as information on adverse events related to uses outside the currently approved indications for use, delayed onset of adverse events, and less frequent but severe or unexpected adverse events?

Current clinical study designs for pre-market approval of dermal fillers

FDA has collated information on the clinical study designs that have been approved for pre-market evaluation of dermal filler devices. These studies have key similarities but also select differences, such as in the types of evaluation methods and validated scales that have been used to determine device effectiveness. FDA is interested in gathering information to understand if the post-market experience of dermal fillers has been consistent with and predicted by the clinical

data collected in studies to support FDA pre-market approval. After review of information presented by FDA, you will be asked to respond to and discuss the following questions.

7. Device effectiveness has been evaluated using validated wrinkle severity and global aesthetic improvement scales.
 - a. Are these evaluation methods for determining device effectiveness in clinical studies adequate?
 - b. Are particular evaluation methods more predictive of device effectiveness in the general population than others?
 - c. What is the value of masked versus non-masked evaluation, and live versus photographic evaluation?

8. Are the evaluation methods used to determine device safety adequate? Should current safety evaluations be expanded to include:
 - a. Larger studies to detect adverse events that may occur at lower frequency?
 - b. Studies of longer duration to detect delayed onset of adverse events?
 - c. Histological evaluation of biopsy samples?

9. Do the inclusion/exclusion criteria utilized in these studies allow for collection of safety and effectiveness data that are consistent with and predictive of your experience with dermal fillers in the post-market setting (e.g. personal practice, published literature, and FDA presented data)?

10. Does the exclusion from clinical study participation of subjects who have had recent cosmetic procedures (e.g. other dermal fillers, laser and chemical treatments, botulinum toxin type A, etc.) impact the manufacturer's ability to collect complete safety information?

11. Are current methods for determining sensitization potential adequate (i.e. pre-clinical study methods such as Magnusun-Kligman Maximization test method and clinical study method of evaluating adverse events in subjects after two dermal filler injections several months apart)? As an individual has the potential to receive numerous injections of dermal fillers within a lifetime, should the study methods for determining sensitization potential be designed to be more reflective of the frequency of dermal filler injection in actual clinical use?

12. If a post-approval study is recommended for current indications for use, please recommend approaches or strategies that would properly evaluate the safety of dermal fillers in this population and suggest the appropriate study design, comparison group, length of follow-up, validated assessment method, and safety endpoints.

Clinical study design in support of new indications for use for dermal fillers

There is much evidence in peer-reviewed publications as well as in various forms of media that dermal filler devices are being used to fill and contour many areas of the face and body. FDA predicts that sponsors may seek approval for these tissue augmentation indications in addition to the indication of correction of facial wrinkles. Therefore, FDA would like to take this

opportunity to ask the panel to discuss the evaluation of safety and effectiveness of potential new indications for use for dermal fillers. After review of information presented by FDA, you will be asked to respond to and discuss the following questions.

13. Injection into nasolabial folds has been considered representative of dermal filler use to correct moderate to severe wrinkles. Can the use of dermal fillers for augmentation of tissue volume and for recontouring of tissues, such as non-surgical rhinoplasty, lip augmentation, under eye injection, and hand volume restoration be considered an extension of filler use for wrinkle correction? What areas of the face would be considered as having tissue structure and physiology that are dissimilar to nasolabial folds?

14. Can the safety and effectiveness data collected from randomized, controlled clinical trials that studied the injection of dermal fillers into nasolabial folds be considered predictive of their safety and effectiveness for any of the new indications? Or are such uses dissimilar to use in nasolabial folds such that they would warrant new clinical studies?

15. In design of clinical studies for these new indications of tissue augmentation and recontouring, such as non-surgical rhinoplasty, lip augmentation, under eye injection, and hand volume restoration:

- a. What safety and effectiveness endpoints would you recommend should be considered?

- b. What are some clinical issues, both short and long term, which would need to be addressed? (For example device migration, local tissue response and chronic inflammatory response)
 - c. What would be the most appropriate control? Should FDA consider controls that are accepted as current standard of care? Specifically, for lip augmentation, what treatment could be considered as standard of care and thus considered as a possible control?
 - d. When there is potential for larger volume and/or repeated injection of dermal fillers over a relatively short period of time (< 6 months), would acute and long-term systemic toxicity studies be warranted?
16. If a post-approval study of new indications for use of dermal fillers is recommended, please recommend approaches or strategies that would properly evaluate the safety of these devices and suggest the appropriate study design, comparison group, length of follow-up, validated assessment method, and safety endpoints.